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Review

Glycemic effects of simvastatin: Where do we stand?

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In clinical practice, simvastatin is usually used in the treatment of dyslipidemia patients and those at risk of or with established cardiovascular disease. However, previous studies have shown that simvastatin has the potential to affect glycemic parameters as it reportedly reduced insulin secretion and sensitivity. The exact mechanism by which simvastatin affects glycemia is still unknown, but previous studies have postulated the involvement of the glucose-insulin secretion mechanism. This review focuses on the effects of simvastatin, either alone or in combination with other lipid lowering agents, antidiabetics and antihypertensives, on glucose homeostasis. Some studies have reported that simvastatin might impair the levels of glucose metabolism markers in the blood while others have reported no effect or improvement in glycemia.

Keywords: Simvastatin/effects. Glucose. Insulin secretion. Insulin sensitivity. Diabetes. Concurrent medications.

INTRODUCTION

Statins or 3-hydroxyl-3 methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors are used worldwide to treat dyslipidemia and also as part of the management of patients who have high risk of developing or established cardiovascular events resulting from type 2 diabetes mellitus (T2DM) or hypertension (Grover, Luthra, Maroo, 2014; Perreault *et al*., 2009). T2DM patients have a two- to four-fold increase in risk of cardiovascular disease as compared to the general population (Colhoun *et al*., 2004). In addition, these patients tend to have high levels of triglyceride, low levels of high-density lipoprotein (HDL) with smaller and denser low-density lipoprotein (LDL) particles that promote atherogenesis (Vijan, Hayward, 2004).

The key action of statins are by inhibition of the HMG-CoA reductase enzyme, hence reducing mevalonate synthesis and subsequently inhibits several other isoprenoid pathways as well as cholesterol synthesis (Gazzerro *et al*., 2012; Sirtori, 2014) (Figure 1). Currently, there are several types of statins available in the market, such as simvastatin, atorvastatin, lovastatin, fluvastatin, rosuvastatin and pravastatin. Cerivastatin has been withdrawn from the market after 52 deaths were reported due to kidney failure as a result of rhabdomyolysis (Furberg, Pitt, 2001).

In the United States, data from the National Health and Nutrition Examination Survey 2011-2012 showed that among adults aged 40 years and above who were using lipid-lowering drugs, 83% were using a statin, 10% a combination of a statin and a non-statin and 7% non-statin. Simvastatin was the most commonly used statin (42%), followed by atorvastatin (20.2%), pravastatin (11.2%), rosuvastatin (8.2%) and lovastatin (7.4%) (Gu *et al*., 2015).

Simvastatin or its brand name *Zocor* (Al-Foraih, Somerset, 2016) is one of the most commonly used statins because of its effectiveness in reducing LDL cholesterol levels, produces fewer adverse effects, and is more affordable compared with other statins. Simvastatin is a semi-synthetic derivative of lovastatin which is obtained from a fermented product of *Aspergillus terreus* (Manzoni, Rollini, 2002). Most patients are prescribed simvastatin at dosages of 10, 20, or 40 mg/day. However, the use of simvastatin at 80 mg/day is restricted because of a high

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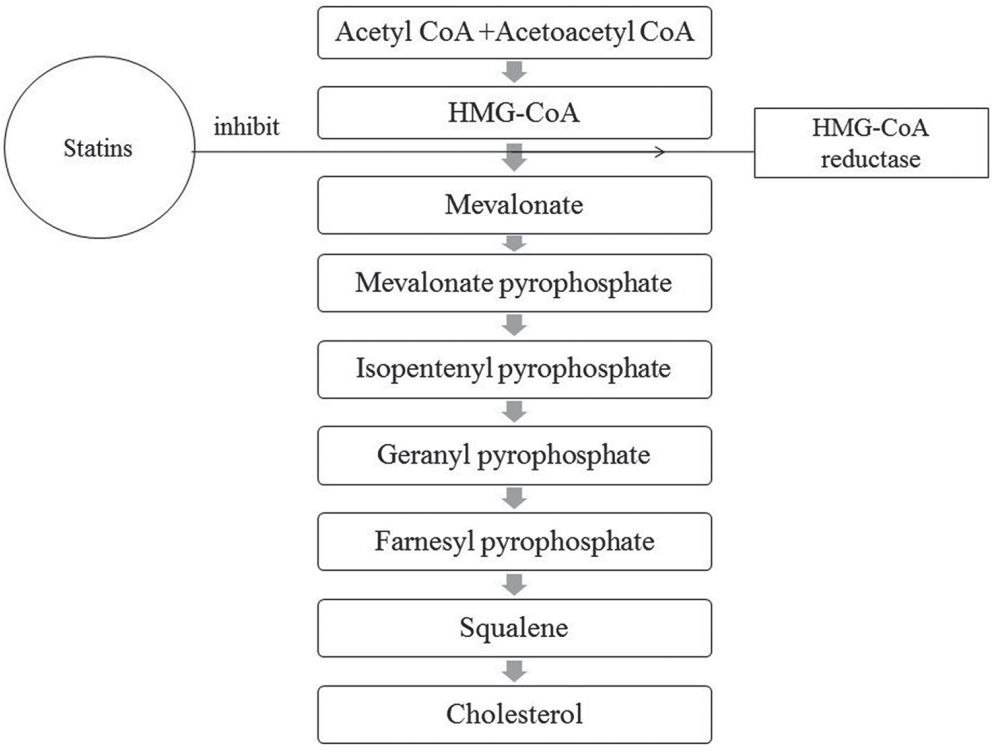

FIGURE 1 - Inhibition of the cholesterol synthesis pathway by statins.

risk of muscle injury (FDA, 2011).

The efficacy of simvastatin in reducing the risk, morbidity, and mortality of cardiovascular events has been demonstrated in various studies, such as the Scandinavian Simvastatin Survival Study (Pedersen *et al*., 1998), the Heart Protection Study (Heart Protection Study Collaborative Group, 2002), the Study of the Effectiveness of Additional Reduction in Cholesterol and Homocysteine (SEARCH) Collaborative Group (Meade *et al*., 2010) and others (Ceriello, 2002; Dobs *et al*., 2008; Foody *et al*., 2008). However, some studies have reported association between statins and glycemia, but such effects are controversial and conflicting ranging from adverse, neutral to beneficial. In diabetics, simvastatin has been shown to worsen glycemic control and insulin secretion (Bellia *et al*., 2012), improve insulin resistance (Paolisso *et al*., 2000) or to have no effect on glucose levels (Farrer *et al*., 1994; Szendroedi *et al*., 2009).

In terms of solubility, statins can be classified into water-soluble (hydrophilic) and lipid soluble (lipophilic). Atorvastatin, fluvastatin, lovastatin, and simvastatin are lipophilic statins, while rosuvastatin and pravastatin are hydrophilic statins (Igel, Sudhop, Bergmann, 2002). For lipophilic statins, it can diffuse through the plasma membranes of extrahepatic cells (for example beta cells, adipocytes and skeletal muscle cells), which can result in a diabetogenic effect (Aiman, Najmi, Khan, 2014; Schachter, 2005). As simvastatin is a lipophilic statin, it has the potential to reduce insulin secretion and sensitivity (Koh *et al*., 2009).

Effect of simvastatin on glucose metabolism: *in vitro* studies

The exact mechanisms underlying the effect of simvastatin on glycemia are still unknown. However, previous studies have implicated the inhibition of glucose-stimulated insulin secretion. Several experimental studies have indicated how simvastatin affects glucose metabolism (Figure 2).

The effect of statins (simvastatin, simvastatin acids, and pravastatin) on β cell function has been investigated in rat pancreatic β cells. Cytosolic calcium (Ca^{2+}) concentration is an important component in the regulation of pancreatic β cells (De Marchi *et al*., 2014). A reduction in the cytosolic Ca^{2+} concentration leads to impairment of insulin secretion. In the study by Yada *et al*. (1999) has demonstrated that simvastatin inhibited β cell L-type Ca^{2+}channels and reduced insulin secretion but pravastatin did not. After administration of simvastatin for 20 seconds, L-arginine and potassium chloride-induced insulin release were inhibited (Yada *et al*., 1999).

The mechanisms by which simvastatin impairs insulin secretion have been elucidated using mouse islet

β cell lines, MIN6. Compared to normal control cells, simvastatin significantly inhibited insulin secretion in a dose-dependent manner. The inhibition of insulin secretion was indirectly caused by reduced levels of glucose transporter 2 (GLUT2). Simvastatin reduced the adenosine triphosphate (ATP) levels in MIN6 cells, increased the ATP-sensitive potassium channel (KATP) current and reduced the L-type - Ca^{2+} current. Simvastatin may also reduce insulin secretion by increasing the rectifier potassium channel (Kir6.2) current while simultaneously decreasing the voltage-dependent Ca^{2+} channel 1.2 (Cav1.2) current, which leads to inhibition of membrane cell depolarization and inhibition of calcium influx (Zhou *et al*., 2014).

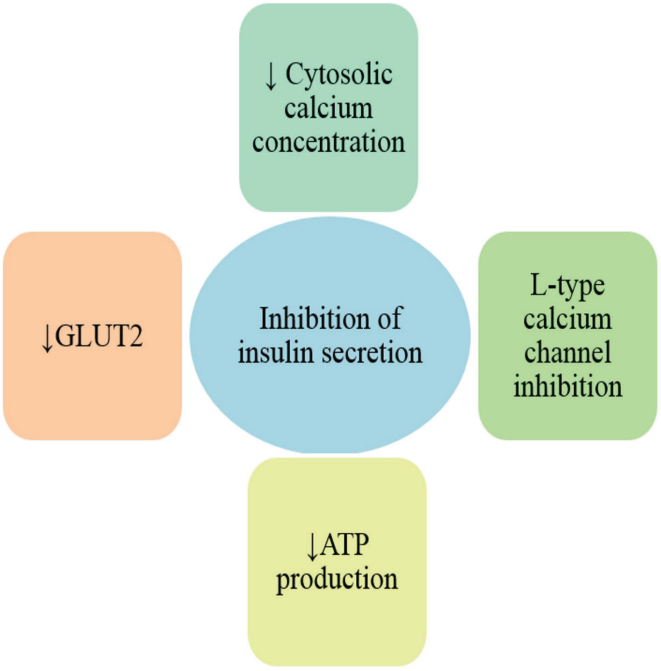

FIGURE 2 – Previous experimental findings on the effect of simvastatin on glucose-insulin secretion.

Glycemic effect of simvastatin: human data

Simvastatin has been reported to increase plasma glucose levels and reduce insulin sensitivity. A few studies have measured the effect of simvastatin treatment on glucose homeostasis (Table I). In a study by Koh *et al.* (2008) reported that simvastatin improved flow-mediated dilation, but reduced adiponectin levels and insulin sensitivity in hypercholesterolemia patients (Koh *et al*., 2008). Patients who were on simvastatin 80 mg/day had a 7% increase in mean plasma glucose levels after 2 months of treatment. Meanwhile, those who were on simvastatin 10, 20, 40, or 80 mg/day had increased insulin secretions relative to the baseline after 2 months of treatment, which is indicative of deterioration in insulin sensitivity. The same study also demonstrated that there was a slight reduction in insulin sensitivity in the simvastatin-treated group, as measured using the quantitative insulin sensitivity check index (QUICKI) (Koh *et al*., 2008). A separate study by the same authors showed significant reductions in insulin sensitivity and plasma adiponectin levels in hypercholesterolemia patients after taking simvastatin 20 mg/day for 2 months. However, there were no significant differences in insulin or glucose levels compared to baseline (Koh *et al*., 2015).

A study in which patients were selected randomly to receive either simvastatin 20 mg/day or rosuvastatin 20 mg/day showed that there was no effect of simvastatin on insulin sensitivity and glycemic control after 4 weeks of treatment (Bellia *et al*., 2010). However, another study by the same authors reported that the simvastatin and rosuvastatin treatments worsen fasting blood glucose (FBG) and A1C levels after 12 months without affecting insulin sensitivity (Bellia *et al*., 2012). On the same note, a study by Sen *et al*. (2002) found that in simvastatin group, A1C levels were significantly increased at follow-up at 90 and 180 days compared to day 1 (Sen *et al*., 2002).

Conversely, some studies have reported a lack of association between simvastatin treatment and blood glucose levels. After 90 days of simvastatin treatment, the homeostasis model assessment - insulin resistance (HOMA-IR) values and FBG levels remained unchanged in patients with isolated hypercholesterolemia, even though there were improvements in plasma lipid levels (Krysiak, Okopien, 2013a). As for T2DM patients, some studies have reported no significant changes in glucose parameters after simvastatin treatment (Farrer *et al*.,1994; Hwu *et al*., 1999). Szendroedi *et al*. (2009) reported that there was no effect of simvastatin on insulin sensitivity, fasting insulin levels or HOMA-B levels (Szendroedi *et al*., 2009). In addition, a study by Hydrie *et al*. (2007) found after receiving simvastatin for 3 months, there were no significant differences in HOMA-IR values compared to baseline. However, 20 patients with T2DM who were having insulin resistance with HOMA-IR values of more than 2.8 at the beginning of the study demonstrated improvements in insulin sensitivity after receiving simvastatin (Hydrie *et al*., 2007).

Simvastatin and new-onset Diabetes

The Heart Protection Study has suggested that there was no association between simvastatin use and new-onset diabetes, although previous studies have reported that statins

TABLE I - The effect of simvastatin on glucose metabolism markers in human data

Study design	Country	Subjects	N	Mean follow-up	Method	Outcome (compared with baseline)				
						A1C	Glucose	Insulin	Insulin sensitivity	Adiponectin
Randomized, double blind, placebo controlled parallel study (Koh *et al*., 2008)	Korea	Hypercholes-terolemia	156	2 months	Each 32 patients given either placebo, SIM 10, 20, 40 or 80 mg/day	Not measured	SIM 80 mg/ day increase glucose level	SIM 10, 20, 40 and 80 mg/day increase insulin level	SIM 10,20, 40 and 80 mg/day reduce insulin sensitivity	SIM 10, 20, 40 and 80 mg/day decrease plasma adiponectin
Randomized, single-blind, placebo-controlled, parallel study (Koh *et al*., 2015)	Korea	Hypercholes-terolemia	203	2 months	Each 51 patients receive either placebo, EZE 10 mg + SIM 10 mg (Vyto10), EZE 10 mg + SIM 20 mg (Vyto20) or SIM 20 mg alone once daily	SIM 20 mg no different	SIM 20 mg no different	SIM 20 mg group not significant change insulin level	SIM 20 mg group reduce the insulin sensitivity	SIM 20 mg group significantly reduce plasma adiponectin level
Randomized, single-blind, parallel intervention study (Bellia *et al*., 2010)	Italy	Patients with middle aged with T2DM and mild treated dyslipidemia	29	4 weeks	Patients receive either ROS 20 mg/day or SIM 20 mg/day	Not measured	No effect in both groups	No effect in both groups	No effect in both groups	No effect in both groups
Randomized, single-blind with two period (Bellia *et al*., 2012)	Italy	Well controlled T2DM patients	27	12 months	Patients receive either ROS 20 mg/day or SIM 20 mg/day for 6 months and switch the treatment for following next 6 months	Both groups worsen A1C	Both groups increase FBG	No changes	No effect in both groups	Not significant increase
Double blind randomized placebo-controlled study (Sen *et a.l*., 2002)	India	T1DM and T2DM with diabetic retinopathy	50	180 days	Patients receive either SIM 20 mg/day or placebo	A1C in SIM group increase throughout the follow-up at 90 days and 180 days	No significant changes in FBG	No significant changes	Not measured	Not measured
Randomized study (Tsutamoto *et al*., 2009)	Japan	Non-ischemic chronic heart failure	71	2.2 ± 0.15 years	Patients receive either SIM 5 mg/day (n = 35) or ROS 2.5 mg/day (n = 36)	Slightly increase in SIM group & decrease in rosuvastatin group	Not measured	Not measured	Not measured	No changes in SIM group but increase in ROS group
Randomized, case-control study (Krysiak, Okopien, 2013a)	Polland	Isolated hypertriglyceri-demia	39	3 months	Patients receive placebo or SIM 40 mg/day	Not measured	Both groups not significant	Not measured	Both groups not significant	Not measured
Double blind placebo controlled study (Farrer *et al*., 1994)	United Kingdom	Patients with T2DM dyslipidemia and mild hypertriglyce-ridemia	70	6 months	Patients randomized to receive placebo or SIM	No significant changes	No significant changes	No significant changes	Not measured	Not measured
Randomized, double-blind, placebo-controlled and two-period crossover study (Hwu *et al*., 1999)	Taiwan	Patient T2DM with hypercholes-terolemia	19	6 months	Patients receive either SIM 20 mg/day or placebo for 3 months and exchange the treatment for subsequent 3 months	No effect in SIM group	No effect in SIM group	Not measured	No effect in SIM group	Not measured
Randomized, double-blind, placebo-controlled, single center study (Szendroedi *et al*., 2009)	German	Non-obese T2DM patients	30	2 months	Patients given placebo or SIM 80 mg/day	No significant changes	Not measured	No significant changes	No significant changes	Not measured
Randomized, case control study (Hydrie *et al*., 2007)	Pakistan	Patients with T2DM	100	3 months	50 patients receive SIM 40 mg/day as case and 50 patients as control group	Not measured	No significant changes	No significant changes	No significant changes	Not measured

Abbreviation: SIM (simvastatin); EZE (ezetimibe); ROS (rosuvastatin); T1DM (type 1 diabetes mellitus); T2DM (type 2 diabetes mellitus). Significant value $p < 0.05$

might induce the new-onset of diabetes. Among 14, 573 subjects without diabetes at study entry, it was noted that there was no significant difference in number of new-onset diabetes between the simvastatin group (4.6%) and the placebo group (4.0%). After follow-up for 4.6 years, among 1087 subjects who had diabetes at study entry, there was no significant difference in increased A1C among treatment groups (Heart Protection Study Collaborative Group, 2003).

However, the Study of Effectiveness of Additional Reductions in Cholesterol, Homocysteine (SEARCH) trial showed that there was a slight increase in new-onset diabetes with high dose simvastatin, 80 mg/day (11.6%) compared to low dose, simvastatin 20 mg/day (10.9%) (Armitage *et al*., 2010) (Table II).

Effect of simvastatin and concurrent medications on glycemic control

Certain patients, like those with metabolic syndrome and T2DM, require combinations of lipid lowering drugs because the use of simvastatin alone may fail to result in optimal lipid targets. Fenofibrate and niacin are the lipid lowering agents which are most often prescribed together with statins (Cannon, 2008). However, these concomitant drugs may increase the risk of drug-drug interaction with regards to glycemic effects, as shown in Table III.

Niacin therapy is known to have beneficial effects in patients with dyslipidemia as it increases HDL cholesterol levels and at the same time reduces triglyceride and LDL cholesterol levels. However, niacin has the potential to increase blood glucose levels (Bays, 2008; Sazonov *et al*., 2013; Zhao *et al*., 2004). In a study by Vittone *et al*. (2007), it was found that three years' usage of niacin in combination with simvastatin had a slight adverse effect on glycemic control, whereby FBG was increased by 3%, fasting insulin was elevated by 19%, and insulin sensitivity was reduced by 10% compared to baseline results (Vittone *et al*., 2007). As such, even though niacin when used alone or in combination with a statin gives beneficial effects to T2DM patients (in terms of achievement of target lipid levels), glucose levels should be monitored in those who are on long-term treatment (Ding, Li, Wen, 2015).

In general, fibrates reduce plasma triglyceride levels by 30-50%, reduce LDL cholesterol levels by up to 20%

TABLE II - Comparison of relative risk of new-onset diabetes with simvastatin use

Study's Name	Subjects	Mean follow-up	Method	Relative risk of NOD (95% CI)
Heart Protection Study (HPS) (Heart Protection Study Collaborative Group, 2003)	Patients with diabetes (5, 963) and patient occlusive arterial disease with non-diabetes (14, 573)	4.6 years	Patients randomized to receive either simvastatin 40 mg/day or matching placebo	Simvastatin vs. placebo 1.14 (0.98-1.33)
Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) (Armitage *et al*.,2010)	12, 064 patients with history of myocardial infarction	6.7 years	Patients randomized to receive either low dose, simvastatin 20 mg (6,033 patients) or high dose 80 mg (6,031 patients) daily	High dose vs. low dose 1.07 (0.95-1.19)

Abbreviation: NOD (New-onset diabetes)

TABLE III - Summary effects of simvastatin in combination with other lipid lowering medications based on previous studies

Authors	Combination lipid lowering drug	Finding (compared to baseline)
(Vittone *et al.*, 2007)	Niacin + simvastatin	↑ FBG, ↑ fasting insulin, ↓ insulin sensitivity
(Derosa *et al.*, 2009)	Fenofibrate + simvastatin	↓ A1C, no significant changes in fasting glucose, fasting insulin, post-prandial glucose
(Koh *et al.*, 2015)	Ezetimibe + simvastatin (Vyto 10)	↓ Fasting insulin, ↑ adiponectin, ↑ insulin sensitivity

and increase HDL cholesterol levels by 5-15% (Chapman, 2003; National Cholesterol Education Program, 2002). In contrast to niacin, fenofibrate is often used with simvastatin in T2DM patients to achieve target lipid levels because fibrates do not lead to the worsening of blood glucose levels. The simvastatin-fenofibrate combination has been shown to be significantly more effective than simvastatin alone (Grundy *et al*., 2005). A study whose objective was to determine the effectiveness of fenofibrate alone, simvastatin alone and both drugs combined recruited 241 patients with T2DM and dyslipidemia who have never been prescribed lipid lowering medications before. The patients were divided into three groups; one received fenofibrate 145 mg/day, another received simvastatin 40 mg/day, and the remaining received a combination of the aforementioned drugs. Glucose and lipid profiles were evaluated at baseline, 6 and 12 months. As expected, total cholesterol, LDL cholesterol, and triglyceride levels decreased while HDL cholesterol increased. In patients treated with simvastatin alone, there was no difference between baseline A1C levels and those at 12 months. However, A1C levels were significantly decreased in the other two groups. After 6 and 12 months of treatment, there were no significant differences in FBG, postprandial glucose and fasting plasma insulin levels in all three groups (Derosa *et al*., 2009).

Ezetimibe is a LDL cholesterol-lowering drug that acts by inhibiting the absorption of dietary cholesterol in the small intestine (Ahmed, Byrne, 2010). In a randomized double-blinded study, T2DM patients received stable doses of thiazolidinediones (rosiglitazone 2-8 mg/day or pioglitazone 15-45 mg/day) for at least 3 months and simvastatin 20 mg/day for 6 weeks prior to the study. Patients were then randomized to receive either ezetimibe 10 mg/day (n=104) or an increased dose of simvastatin 40 mg/day (n=110) for 24 weeks. The results showed that there were no significant differences between treatment methods with regards to FBG, fasting plasma insulin, and A1C levels. However, LDL cholesterol levels were reduced to a greater extent in patients who received additional ezetimibe 10 mg/day or simvastatin 20 mg/day compared to those who received a doubled simvastatin dose (40 mg/day) (Gaudiani *et al*., 2005). Another study found that 2 months after the administration of combined simvastatin 10 mg and ezetimibe 10 mg (Vyto10) to patients with dyslipidemia, fasting insulin was significantly reduced while plasma adiponectin and insulin sensitivity were increased relative to the baseline (Koh *et al*., 2015).

Patients with T2DM may have multiple comorbidities that necessitate the concomitant administration of statins with other drugs. Clinical studies have shown that a combination of simvastatin with metformin and pioglitazone results in improved glycemic control (Table IV). In T2DM patients, metformin is the recommended first-line pharmacological treatment after

TABLE IV - The effect of concurrent medications in combination with simvastatin (oral antidiabetic agents)

Concurrent medication	Subjects	Country	N	Mean follow-up (months)	Method	Outcome				
						Fasting glucose	Fasting insulin	A1C	Insulin sensitivity	Adiponectin
Metformin (Krysiak, Okopien, 2013b)	IFG patients treated with simvastatin at least 3 month	Poland	48	3	Patient randomized received MET or placebo for the next following 90 days	MET + SIM group approach near significant decrease FBG compared to before randomization ($p = 0.071$)	Not measured	MET + SIM group significant reduce A1C compared to baseline and placebo ($p < 0.001$)	MET + SIM group had improvement in HOMA-IR ($p < 0.001$)	Not measured
Pioglitazone (Forst *et al.*, 2007)	Non-diabetic patients with cardiovascular risk	Germany	125	3	Patients randomized received PIO + placebo, PIO + SIM, SIM + placebo. Treatment started with PIO 30 mg or and SIM 20 mg. After 2 weeks increase dosage to PIO 45 mg or and SIM 40 mg	FBG reduce in group treated with PIO and PIO + SIM	Reduce in group treated with PIO and PIO + SIM	Not measured	HOMA score improved in group treated with PIO and PIO + SIM	Adiponectin increase in PIO and PIO + SIM group, while reduce in group treated with SIM

Abbreviation: MET (metformin); SIM (simvastatin); PIO (pioglitazone)

lifestyle interventions fail to result in adequate glycemic control (Rojas, Gomes, 2013). Krysiak *et al.* (2013b) demonstrated that metformin, when administered to simvastatin-treated patients with impaired fasting glucose levels, reduced HOMA-IR values by approximately 55% and A1C levels by 11% (Krysiak *et al.*, 2013b).

Pioglitazone – a thiazolidinedione that works by enhancing insulin sensitivity –improves A1C levels and is beneficial in reducing free fatty acid and triglyceride levels as well as increasing HDL cholesterol (Herz *et al*., 2003; Kipnes *et al*., 2001). In a double-blinded study, pioglitazone alone and the combination of pioglitazone and simvastatin significantly improved glucose levels, insulin levels, and HOMA score. No such changes were seen in the simvastatin treatment group. In addition, it was reported that the pioglitazone-simvastatin combination was better for lowering the risk of cardiovascular events when compared to either of the drugs used alone (Forst *et al*., 2007).

Hypertension and hypercholesterolemia are two major health issues that contribute to increased cardiovascular disease risk (Dalal *et al*., 2012), and the patients are commonly treated with statins and antihypertensive agents. As shown in Table V, the effect of combined simvastatin and antihypertensive medications has been investigated, and it was found that fasting plasma

TABLE V - The effect of concurrent medications in combination with simvastatin (antihypertensive agents)

Concurrent medication	Subjects	Country	N	Mean follow-up (month)	Method	Outcome				
						Fasting glucose	Fasting insulin	A1C	Insulin sensitivity	Adiponectin
Perindopril or barnidipine (Derosa *et al.*, 2015)	Normocholesterolemic, hypertensive patients with nonalcoholic hepatic steatosis	Italy	149	12	Patients were on perindopril 5 mg/day or barnidipine 20 mg/day for 6 months and added with SIM 20 mg/day for subsequent 6 months	No significant changes in both group	No significant changes in both group	Not measured	Not measured	Increase in barnidipine + SIM group compared to baseline ($p < 0.05$)
Losartan (Koh *et al.*, 2004)	Hypercholesterolemia with hypertensive patients	Korea	47	3 treatment arm (2 months for each) and 2 washout period (2 months)	Patients were randomized receive either SIM 20 mg + placebo, SIM 20 mg + losartan 100 mg or losartan 100 mg + placebo daily	No significant changes in three group	No significant changes in three group	Not measured	Losartan + SIM and losartan group significantly increase QUICKI	Increase in combination losartan + SIM group ($p < 0.001$) and losartan alone ($p = 0.002$)
Ramipril (Koh *et al.*, 2005)	Hypercholesterolemia with T2DM	Korea	53	3 treatment arm (2 months for each) and 2 washout period (2 months)	Patients were randomized receive either SIM 20 mg + placebo, SIM 20 mg + ramipril 10 mg or ramipril 10 mg + placebo daily	No significant changes in three group	No significant changes in three group	Not measured	Increase QUICKI in SIM + ramipril group and ramipril alone group	Increase in SIM + ramipril group and ramipril alone group
Lisinopril (Kaminsky *et al.*, 2010)	Atherosclerosis and moderate hypertensive	Russia	32	24	Patients were randomized receive either lisinopril 10-20 mg/day or lisinopril 10-20 mg added with SIM 20 mg daily	No significant changes in both group	Not measured	Not measured	Not measured	Not measured

Abbreviation: SIM (simvastatin)

insulin and FBG levels were not affected by perindopril-simvastatin or barnidipine-simvastatin regimens (Derosa *et al*., 2015). However, Koh *et al.* (2004) found that losartan alone or in combination with simvastatin resulted in a significant increase in insulin sensitivity and plasma adiponectin levels relative to the baseline, and that the difference was greater when compared to simvastatin alone (Koh *et al*., 2004).

CONCLUSIONS

In vitro studies have identified possible mechanisms by which simvastatin affects glucose metabolism. These include the inhibition of insulin secretion, possibly by decreasing GLUT2 activity, reducing ATP production, inhibiting L-type Ca^{2+} channels and decreasing cytosolic Ca^{2+} concentrations. Some studies have reported that simvastatin may impair glucose metabolism whereas other studies reported no effect or improvement of glucose metabolism.

Even though statins are beneficial in reducing the risk of cardiovascular events, its glycemic effect on patients should be monitored by periodically evaluating blood glucose levels regardless of whether the patients have diabetes or otherwise. Further studies are required to investigate the possible synergistic effects of statins with concurrent medication on glycemia, especially in patients with multiple comorbidities. Although the benefits of statins have been shown to outweigh its risks, it is important that glycemic control in patients is monitored for potential drug interactions between statins with the concurrent medications used. Besides that, further studies are recommended to determine whether or not the dose and duration of statin use could affect the glycemic control.

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DECLARATION OF INTEREST STATEMENT

The authors report no conflicts of interest.

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